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SERO-BACTERIOLOGICUM
UNIVERSITATIS**

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Helsingfors

Professor J. Lederberg
Department of Genetics
Stanford University School of Medicine
Stanford, California

Dear Professor Lederberg,

When a new theory has been developed it is easy to present small modifications and "equally probable possibilities" which may have been taken into account but not presented by the original author. I guess that a number of such suggestions will be presented in consequence of your theory of antibody production, and I shall present one. Your propositions A6-A9 are written below and the modified points are underlined.

A6. The immature antibody-forming cell is hypersensitive to an antigen-antibody combination : it will be suppressed if it encounters a homologous antigen at this time.

A7. The mature antibody-forming cell is reactive to an antigen-antibody combination : it will be stimulated if it encounters a compound more or less complementary to the "antibody" produced by it at this time. The stimulation comprises the acceleration of protein synthesis and the cytological maturation which mark a "plasma cell". The stimulation is the more effective the more perfect is the complementariness between ~~between~~ the two compounds.

A8. Mature cells proliferate extensively under antigenic stimulation and because there is a continuous selection for the cells that produce the "best fitted" antibodies they generate large clones genotypically preadapted to produce the homologous antibody.

A9. After disappearance of the antigen the selection ends and the cell population begins to "mutate back" - stepwise. There remains, however, enough perfect cells or cells which have not mutated many steps away from perfection, and they account for the secondary response.

The present modification is less versatile than the original theory to explain the maintenance of the responsive state of an individual after the initial immunization and the secondary

response. The modification may, however, explain this phenomenon on two grounds: First - it assumes a less mutation rate than the original theory because a completely fitted cell for every possible antigen is not necessary. For this reason the cell clone produced by an immunization is somewhat stable. Secondly - completely fitted cells are not necessary for a secondary response to take place because even the mature cells are capable of mutating.

The modification explains the experience that when an immunization proceeds the antibodies tend to become better complementary to the stimulating antigen (Porter, R.R. Symposium on Protein Structure, edited by A. Neuberger, page 293.), and the similar observation that "incomplete" (late) Rh-antibodies can inhibit "complete" (early) from agglutinating red cells (Race & Sanger: Blood Groups of Man, 3rd Edit., page 169). It also explains the diversity of antibodies in a single antiserum (Talmage, Science 1959:129, 1643)

Some information could perhaps be gained by the following experiment. Animals are immunized by related cross-reacting antigens A and B. Later they are stimulated by antigen A. They produce great amounts of anti-A which cross-reacts with B. If my suggestion is correct, they produce anti-B, too (antibody which reacts better with B than with A). These two related antibodies could perhaps be distinguished by means of gel-diffusion method.

It was a great pleasure to read your article.

Yours truly

Olavi Mäkelä

Olavi Mäkelä, M.D.